IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana REDDY et al. Art Unit: 1625

Application No.: 10/647,449 Examiner: C. C. Chang

Filed: August 25, 2003

For: POLYMORPHIC FORMS OF S-REPAGLINIDE
AND THE PROCESSES FOR PREPARATION THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

SUPPLEMENTAL REPLY BRIEF

This is submitted in response to the Supplemental Examiner's Answer that was mailed on April 21, 2008 for the subject application. As a response is permitted within a two-month period, this paper is being timely filed.

The Supplemental Examiner's Answer referred to Appellants' "supplemental appeal brief filed February 1, 2008." However, the document that was submitted actually was titled as a "Supplemental Reply Brief," and it was submitted on February 5, 2008.

1. Status of the Claims

Claims 1-57 were finally rejected in an Office Action mailed on March 6, 2006. Claims 3, 39, 49, 52 and 55 were canceled in an amendment submitted on December 1, 2005. Accordingly, claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56 and 57 are considered to be the subject of this appeal.

2. Grounds of Rejection for Review on Appeal

A. Whether claims 38 and 40-48 are anticipated under 35 U.S.C. § 102(b) by Grell et al (U.S. Patent No. 5,312,924; "Grell I").

B. Whether claims 1, 34 and 35 are anticipated under 35 U.S.C. § 102(b) by Grell I.

C. Whether claims 1, 2, 4-37, 50, 51, 53, 54, 56 and 57 are unpatentable under 35 U.S.C. § 103(a) over Grell I in view of Grell et al. (*Journal of Medicinal Chemistry.*, 1998, 41:5219-5246; "Grell II"), and H. Brittain, ed. (*Polymorphism in Pharmaceutical Solids*, 1999, pp. 2, 178-179, 185, and 219; "Brittain").

D. Whether claims 8-18 are unpatentable under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement.

3. Argument

The appeal history of this application is extensive, and Appellants have previously submitted an appeal brief and three reply briefs; Appellants continue to rely upon the arguments in all of the previously submitted appeal documents.

The most recent Supplemental Examiner's Answer cited an additional three non-patent documents: an article by G. Zhang et al. in *Journal of Pharmaceutical Sciences*, 92(7), pp. 1356-1366 (2003) (hereinafter, "Zhang"); an article by R. Fasel et al. in *Nature*, Vol. 439, pp. 449-452, 26 January 2006, (hereinafter, "Fasel"); and an article by M. Yokota et al. in *Journal of Chemical Engineering of Japan*, 37(10), pp. 1284-1285 (2004) (hereinafter, "Yokota"). Appellants note that only Zhang appears to antedate the filing of the presently appealed application, and that none of the documents antedates Appellants' priority application filing dates; these documents therefore cannot constitute prior art for the purpose of rejecting Appellants' claims.

The Supplemental Examiner's Answer states that the documents "provide comprehensive description of the prior art … dates from 1848 to date." However, Appellants cannot identify anything in the documents that would relate to their claimed polymorphic forms of the drug compound S-repaglinide, and processes relating thereto.

Zhang pertains to the sodium salt of ibuprofen. The article describes a discovery of multiple polymorphic forms of racemic sodium ibuprofen, and characterizes the possible existing phases of the racemic mixture as a conglomerate and two single-phase systems. The sodium salt of the (S)-ibuprofen enantiomer was also prepared, but was not found to exhibit polymorphism. Therefore, Appellants submit that the article is not useful to support any rejection of their claims.

Fasel reports a study of M- and P-enantiomers of heptahelicene that was deposited onto a particular surface of a copper single crystal. The domains of each enantiomer were mapped in the heptahelicene layer. This does not appear to relate in any manner to Appellants' invention. A statement in Fasel that the concept of chirality dates back to 1848 may or may not be correct, but in any event a relationship of this document to Appellants' claimed polymorphic forms of S-repaglinide is not apparent.

Yokota describes enantiomeric separations of D- and L-asparagine from their racemic mixture. This article describes the work of Louis Pasteur, assertedly published in 1848, to separate crystals of the enantiomers of sodium ammonium tartrate by hand, this being made possible by the differences in crystal habit. Later work by others on assymetric crystallization is also described. Yokota reports a finding that adding a relatively small amount of L-cysteine to a solution of DL-asparagine results in only a crystallization of D-asparagine during the first 10 hours, after which L-asparagine crystals begin to form. Yokota does not discuss any polymorphism of a single enantiomer of any compound, and therefore none of its teachings seem to be relevant to Appellants' claims.

The newly-cited Zhang article clearly supports Appellants' position that the existence of polymorphic forms for a racemic mixture is not predictive of the existence of polymorphic forms for a single enantiomer of that compound. It remains a fact that the polymorphs being specifically claimed by Appellants were not described in any documents that are of record in the present application. It also remains a fact that the existence of polymorphic forms for a given compound cannot be predicted, and there is no established procedure for making a previously unknown polymorphic form of a compound.

The Brittain excerpt that was cited in the Final Rejection to support the rejection under 35 U.S.C. § 103(a) states, on page 2:

> Thus, in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules. As a result, the polymorphic solids have different unit cells and hence display different physical properties, including those due to packing, and various thermodynamic, spectroscopic, interfacial, and mechanical properties, as discussed below [1-3].

Combining this teaching of polymorph property variations with the teachings of the Zhang article and other documents of record in the file, the Appellants' claims cannot reasonably be considered as unpatentable. New polymorphic forms of the single S-enantiomer of repaglinide have now been invented, and they could not possibly have been predicted by those skilled in the art. The claimed processes for preparing the new polymorphic forms also could not have been predicted. There is no possibility of anticipation and there is no *prima facie* case made out for obviousness. The obviousness rejection can only be based on the perfect hindsight that has been provided by Appellants' specification, as evidenced by the uncertainty and unpredictability that characterizes the prior knowledge regarding polymorphism.

The rejection under 35 U.S.C. § 112 was not discussed in the most recent Supplemental Examiner's Answer, and Appellants continue to rely on their previously submitted position relating to this rejection.

There is a discussion in the Supplemental Examiner's Answer asserting that racemic repaglinide exists as a physical mixture of R-crystals and S-crystals. This position is purely speculative and, insofar as Appellants understand it, does not appear to have any relevance to the issues on appeal.

The rejections of claims 1-2, 4-38, 40-48, 50, 51, 53, 54, 56, and 57 under 35 U.S.C. §§ 102(b), 103(a), and 112, first paragraph do not have a proper legal or factual foundation and should be reversed.

Respectfully submitted,

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June 19, 2008

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